REMARKS/ARGUMENTS

Reconsideration of this application and entry of the foregoing amendments are respectfully requested.

The specification has been revised to correct certain obvious clerical errors. As will be clear from a review of Table 2 (page 78), the sequence of the alpha-1-antitrypsin leader sequence is set forth in SEQ ID NO:8, not SEQ ID NO:7, as originally recited on page 80. Further, the sequence of the human albumin leader sequence is set forth in SEQ ID NO:7, not SEQ ID NO:8 as originally recited on page 80. In addition, it will be apparent from a review of Example 13 at page 79, line 30, and from a review of Table 1 of Barash et al (Bioch. Biophy. Res. Comm. 294:33-42 (2002)) (cited at page 78, line 13), that Table 3 on page 81 should read "SP38", rather than "SP38.1" (note that at page 81, lines 13 and 14 it is stated that cells were transfected with plasmids described in Example 13 – as noted above, Example 13 recites "SP38" not "SP38.1"). In view of the above, it will be evident that the revisions made to the specification do not add new matter.

The claims have been revised to define the invention with additional clarity. The revision of claim 1 finds support throughout the application, including in now cancelled original claim 6. The revision of claim 3 finds support in Example 13. Claims 7, 8 and 26 have been revised to depend from claim 1. Claims 13, 17 and 23 have been revised to read human GAA. This revision is fully supported by the disclosure, including original claim 7. Claims 21 and 26 have been revised to address the Examiner's concerns based on indefiniteness. New claims 73, 76 and 77 find support in Examples 13 and 14. New claims 74 and 78 find support throughout the application, including in the claims as originally filed. New claim 75 finds support in

Examples 13 and 14. New claim 79 finds support, for example, in original claim 45. In addition to claim 6, claims 19 and 20 have also been cancelled without prejudice.

The Examiner's comments relating to the priority document are noted. Applicants disagree with the Examiner's assertions regarding the entitlement of the instant claims to the filing date of the priority document and direct attention to the fact that Provisional Application No. 60/441,789 does teach nucleic acids encoding a chimeric polypeptide comprising a secretory signal sequence operably linked to a lysosomal polypeptide (see, for example, pages 41 and 42).

Claims 21 and 26 stand rejected under 35 USC 112, second paragraph, as allegedly being indefinite. Withdrawal of the rejection is submitted to be in order in view of the above-noted claim amendments and comments that follow.

Claims 21 and 26 have been revised in a manner that is intended to address the Examiner's concerns. While the revisions suggested by the Examiner have not been adopted, it is believed that the Examiner will find that the amendments made are appropriate in view of the context in which the referenced phrases appear.

Reconsideration is requested.

Claims 1-18 and 21-29 stand rejected under 35 USC 112, first paragraph, as allegedly being non-enabled. Withdrawal of the rejection is submitted to be in order in view of the above-noted amendments and comments that follow.

The Examiner contends that Table 3 includes results for "SP38.1" but not "SP38". The reference in Table 3 to "SP38.1" is a reference to the sequence of SEQ ID NO:5 shown in Table 2. This is clear from the fact that it is stated at page 81, lines 13-17 that:

> 293 cells were transfected with AAV vector plasmids described in Example 13... . Total hGAA activity was assayed .... These results are depicted in Figure 14 and the relative hGAA secretion is summarized in Table 3. (Underlining added.)

Example 13 refers to "SP38", as does Figure 14. Accordingly, it is obvious that the reference to "SP38.1" in Table 3 is a clerical error and that it should read "SP38". Table 3 has been appropriately amended as indicated above.

The Examiner points out that claim 3 reads "prealbumin" while Table 2 and page 80, line 28 read "albumin".[1] Claim 3 has been revised to read "albumin", consistent with Example 13. The Examiner's comment to the effect that "neither 'prealbumin' or 'albumin' signal sequence is shown in Table 3 to cause increased secretion" is noted. While it is acknowledged that Table 3 does not make specific reference to hGAA secretion with an albumin leader sequence, basis for the Examiner's apparent assertion that the albumin leader sequence does not increase secretion is not seen. In this regard, the Examiner's attention is directed to the Western blot shown in Figure 15 and, specifically, to lanes 4 and 12 which demonstrate the significantly increased secretion of hGAA linked to the albumin signal sequence (compare lanes 4 and 12). The Examiner is requested to clarify the basis for the concern so that Applicants will be in a position to respond.

With respect to claim 9, the Examiner states that the specification does not teach any and all 3' untranslated regions less than 200 nucleotides in length and comprising a segment that is heterologous to the GAA coding region. Further, the Examiner states that he has not identified "one such embodiment that has been characterized as to the effect of the addition". In response,

[1] For the Examiner's information, a precursor form of albumin is cleaved in the Golgi vesicles to produce secreted albumin.

the Examiner is reminded that a patent applicant enjoys the presumption that the invention can be practiced as claimed.[2] The burden is on the examiner to provide evidence as to why such would not be the case. The comments offered by the Examiner here do not constitute such evidence.

Finally, the Examiner contends that the claims should be limited "to what is taught in the specification, namely erythropoietin, α-1-antitrypsin and Factor IX leader sequences replacing residues 1-27 of SEQ ID NO:2".[3] Respectfully, the subject disclosure is far broader than these specifically exemplified embodiments (see, for example, the extensive disclosure relating to lysosomal polypeptides on pages 16-19 and secretory signal sequences on pages 19-25). To require that the claims be limited to the exemplified embodiments would be to unduly restrict Applicants in the scope of protection to which they are rightly entitled, given the breadth of the disclosure provided.

In view of the above, the Examiner is requested to provide proper basis for the rejection or withdraw same.

Claims 1-18 and 21-29 stand rejected under 35 USC 103 as allegedly being obvious over McCown et al. The rejection is traversed.

In rejecting the claims as obvious, the Examiner contends that it would have been obvious to fuse a secretory signal sequence to a lysosomal polypeptide with the expectation that the polypeptide would be secreted. The Examiner further contends that the particular signal sequence used and the identity of the protein to be secreted "are design choices and would have been obvious absent unexpected results".

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[2] New claim 79 makes reference to a specific 3' untranslated sequence.
[3] See new claim 75.

At the outset, Applicants point out that the position taken by the Examiner in rejecting the claims as obvious is wholly inconsistent with the position taken by the Examiner above in rejecting the claims as lacking enablement.

The present invention results, at least in part, from studies designed to test the hypothesis that chimeric lysosomal polypeptides containing an alternative signal peptide could increase the secretion of lysosomal polypeptides from transduced cells and enhance receptor-mediated uptake of lysosomal polypeptides in tissues. As evidenced by the data presented in the application and in a publication by the inventors (Sun et al, Mol. Ther. 14:822 (2006)), replacement of the lysosomal signal peptide (which targets the polypeptide to the lysosome) by other signal peptides, increased secretion from cultured cells (see, for example, Fig. 15 of the application). Further, receptor mediated uptake of the chimeric polypeptide occurred efficiently (see, for example, Table 1 of Sun et al, Mol. Ther. 14:822 (2006)). It is important to note that the uptake was inhibited by mannose-6-phosphate thereby implicating the involvement of mannose-6-phosphate receptors.[4]

Applicants, not the art, showed that secreted lysosomal proteins (as exemplified by hGAA) demonstrate normal migration on Western blot analysis, consistent with unaltered glycosylation and processing of the chimeric protein. Importantly, the normal glycosylation is observed, despite the increased secretion and presumably shortened residence in the Golgi (see Example 14). McCown et al would not have suggested that such would be the case. Accordingly, reconsideration is requested.

[4] Many lysosomal proteins are characterized by the presence of mannose-6-phosphate residues, and in embodiments of the invention, the lysosomal polypeptide comprises mannose-6-phosphate glycosylation.

Claims 1-18 and 21-29 stand rejected under 35 USC 103 as allegedly being obvious over Barash et al. The rejection is traversed.

Applicants point out that this rejection is also inconsistent with the above rejection of the claims under 35 USC 112, first paragraph.

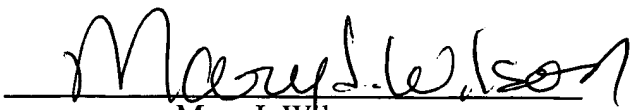
The foregoing comments relating to secretion and uptake are incorporated here by reference.

In addition, and as discussed above, it was Applicants, not the art, who showed that secreted lysosomal proteins demonstrate normal migration on western blot analysis, consistent with unaltered glycosylation and processing of the chimeric protein. Normal glycosylation is observed, despite the increased secretion and presumably shortened residence in the Golgi (see again Example 14). Barash et al would not have suggested that such would be the case. Accordingly, reconsideration is requested.

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: 

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